ANGIOGENESIS

Multi-tasking

c-MYC not only has an integral role in promoting cell proliferation and growth but, as John Cleveland, Troy Baudino and colleagues now report in *Genes and Development*, it also acts as a key regulator of angiogenesis.

Angiogenesis is triggered early in tumour progression by factors that are also crucial for vasculogenesis during embryogenesis. Baudino *et al.* investigated this process in *Myc*^{-/-} embryos, and observed marked defects in vasculogenesis and angiogenesis. Furthermore, tumour size was drastically reduced in *Scid* mice that were injected with *Myc*^{-/-} embryonic stem (ES) cells, indicating that loss of c-Myc impedes tumorigenic potential; indeed, these tumours were also poorly vascularized.

Because the c-Myc-null phenotype resembled that of mice lacking vascular endothelial growth factor (Vegf) or the Vegf receptor Flk1, the authors examined Vegf in their mouse models. Vegf expression was

reduced in *Myc*^{-/-} ES cells and in *Myc*^{-/-} yolk-sac endothelial cells. Addition of Vegf was sufficient to rescue growth defects of *Myc*^{-/-} yolk-sac endothelial cells, but failed to rescue the tumorigenic defects of *Myc*^{-/-} progenitor cells, indicating that c-Myc must have other targets that contribute to tumorigenesis and the angiogenic switch. Indeed, the levels of angiogenic factors thrombospondin-1 and angiopoietin-1 were increased in *Myc*^{-/-} ES cells, with or without overexpression of Vegf, whereas angiopoietin-2 expression was downregulated.

These findings explain why MYC activation is so common in cancer; it gives tumours significant proliferation and survival advantages, and allows tumours to overcome the limits that are imposed by lack of vascularization.

Investigating the role of c-MYC in the regulation of other angiogenic factors and the effect of disrupting c-MYC function for

anti-angiogenesis therapeutics are now important research goals.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Baudino, T. A. *et al.* c-Myc is essential for vasculogenesis and angiogenesis during development and tumor progression. *Genes Dev.* **16**, 2530–2543 (2002)

WEB SITE

John Cleveland's lab:
<http://www.stjude.org/newhp/biochemistry.html>

DRUG RESISTANCE

Damage limitation

In 2000, the National Cancer Institute Anticancer Drug Screen found that the strongest correlation between cancer-related gene expression and resistance to chemotherapeutic agents was for BCL-X_L. In the 4 October issue of *Cell*, Benjamin Deverman and colleagues provide evidence that BCL-X_L has a functional role in resisting apoptosis that is caused by cisplatin and other anticancer agents.

DNA-damaging anticancer therapeutics are effective because they induce apoptosis in tumour cells. As the BCL2 family has a central role in apoptosis, Deverman *et al.* focused on these proteins, and, in particular, on BCL-X_L, which inhibits apoptosis by blocking activity of the proapoptotic branch of the BCL2 family — the BH3-only proteins. They decided to use *TP53*-null, *RB*-null osteosarcoma cells (SAOS-2), which are susceptible to cisplatin-induced apoptosis, to study the apoptosis pathways, because both *TP53* and *RB* are either mutated or functionally inactivated in most tumours.

So, what effect did treatment of SAOS-2 cells with cisplatin have on BCL2 and BCL-X_L? Whereas BCL2 was unaffected in treated cells, BCL-X_L was found to be modified by deamidation — asparagines are converted to a mixture of aspartates and isoaspartates — at two conserved sites, asparagines 52 and 66. This deamidation correlated with the timing of cell

death. Unlike the wild-type BCL-X_L protein, the constitutively deamidated BCL-X_L could not bind to BH3-only proteins and this might contribute to the inability of BCL-X_L to block cisplatin-induced apoptosis in SAOS-2 cells.

If *RB* expression was induced in SAOS-2 cells, BCL-X_L deamidation was suppressed, which allowed cells to resist DNA-damage-induced apoptosis. In addition, the use of BCL-X_L antisense rendered *RB*-expressing SAOS-2 cells sensitive to cisplatin. Deverman *et al.* concluded that SAOS-2 fibroblasts are dependent on BCL-X_L activity for their resistance to cisplatin.

The authors are now concentrating on determining the mechanism by which deamidation is regulated. A better understanding of how the BCL2 family respond to DNA-damaging agents, and their role in drug resistance, should help the development of new therapeutic approaches.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Deverman, B. J. *et al.* Bcl-X_L deamidation is a critical switch in the regulation of the response to DNA damage. *Cell* **111**, 51–62 (2002)

FURTHER READING Amundson, S. A. *et al.* An informatics approach identifying markers of chemosensitivity in human cancer cell lines. *Cancer Res.* **60**, 6101–6110 (2002) | Cory, S. & Adams, J. M. The BCL2 family: regulators of the cellular life-or-death switch. *Nature Rev. Cancer* **2**, 647–656 (2002)

WEB SITE

Steven Weintraub's lab:
<http://dbbs.wustl.edu/rib/Weintraub.html>